PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/70 — A2

(11) International Publication Number: **WO 97/10812**

(43) International Publication Date: 27 March 1997 (27.03.97)

(21) International Application Number: PCT/US96/14331

(22) International Filing Date: 6 September 1996 (06.09.96)

(30) Priority Data:

08/525,867	8 September 1995 (08.09.95)	US
08/708,389	4 September 1996 (04.09.96)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: SUPERSATURATED TRANSDERMAL DRUG DELIVERY SYSTEMS, AND METHODS FOR MANUFACTURING THE SAME

(57) Abstract

Methods are provided for manufacturing transdermal drug delivery systems containing supersaturated drug reservoirs, such that higher drug fluxes are obtained. The methods involve heating the drug reservoir components to a predetermined temperature. Generally, this temperature is higher than the depressed melting temperature of the polymer-drug admixture which will serve as the drug reservoir. In an alternative embodiment, wherein heat treatment of the reservoir components results in a system having two liquid phases, the predetermined temperature is calculated so as to be higher than the melting temperature of the pure drug. Drug reservoirs and novel transdermal delivery systems prepared using the disclosed techniques are provided as well.

SUPERSATURATED TRANSDERMAL DRUG DELIVERY SYSTEMS, AND METHODS FOR MANUFACTURING THE SAME

Technical Field

This invention relates generally to drug delivery, and more particularly relates to supersaturated transdermal drug delivery systems, i.e., transdermal devices containing a supersaturated drug reservoir, and to methods for manufacturing such systems.

Background

The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient and noninvasive way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences -- e.g., gastro-intestinal irritation and the like -- are eliminated as well. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex

None of the art of which applicants are aware describes transdermal drug delivery system having supersaturated drug reservoirs or methods for manufacturing such systems as disclosed and claimed herein. However, the following references are of interest:

U.S. Patent No. 4,409,206 to Stricker relates to a method for preparing transdermal drug delivery systems containing the active substance in an amorphous form. Initially, a polyacrylate film is prepared by solvent casting. A drug solution or suspension is then applied to the film and the solvent is removed by evaporation. There is no disclosure concerning a heating step to dissolve the drug.

U.S. Patent No. 4,746,509 to Haggiage et al. describes transdermal medicaments with the active ingredient dispersed in a drug reservoir in crystalline and/or solubilized form.

U.S. Patent No. 4,832,953 to Campbell et al. describes a method for making drug delivery systems containing liquid drugs capable of forming crystalline hydrates. The drug delivery systems are heated above the melting temperature of the pure drug, after preparation of the systems, to prevent crystalline hydrate formation.

U.S. Patent No. 4,883,669 to Chien et al. describes a transdermal drug delivery system for the administration of estradiol, wherein drug is microdispersed in a polymeric matrix disc layer which serves as the drug reservoir. The reservoir components are heated to a relatively low temperature, below the melting point of estradiol, during device manufacture.

U.S. Patent No. 5,332,576 to Mantelle describes preparation of compositions for topical application, wherein drug is added to certain components, not including the bioadhesive carrier, and

It is another object of the invention to provide a method for making such drug delivery systems, which method involves heating the components of the drug reservoir, during manufacture, to a carefully predetermined temperature, such that a supersaturated reservoir is produced.

It is another object of the invention to provide a transdermal system prepared using the aforementioned method, which comprises a laminated composite of a backing layer and a contact adhesive layer which is supersaturated with drug and serves as both the drug reservoir and the basal surface which contacts the skin or mucosal tissue during use.

It is still another object of the invention to provide a transdermal system prepared using the aforementioned method, which comprises a laminated composite of a backing layer, a contact adhesive layer which serves as the basal surface and contacts the skin or mucosal tissue during use, and, incorporated therebetween, a polymeric matrix which is supersaturated with drug and serves as the drug reservoir.

It is yet another object of the invention to provide a transdermal device prepared using the present method, comprising a laminated composite of a backing layer, a drug reservoir comprising a polymeric matrix supersaturated with drug, and a peripheral adhesive ring for affixing the device to the skin during use.

It is a further object of the invention to provide such methods and transdermal systems in which the drug to be delivered is one that is capable of phase separation into a low thermodynamic activity form such as a crystalline structure.

It is yet a further object of the invention to provide such methods and transdermal systems in

first liquid phase comprising primarily polymeric material, and a second liquid phase comprising primarily drug formulation, wherein the predetermined temperature is such that it is higher than the actual melting temperature of the pure drug contained in the drug formulation; and (c) cooling the heated admixture prepared in step (b) to form the drug reservoir, wherein the relative quantities of drug and polymeric material are such that the drug reservoir contains on the order of 0.1 wt.% to 20 wt.% drug.

Methods for manufacturing transdermal systems are provided as well, comprising preparing a laminated composite of a supersaturated drug reservoir, a backing layer which serves as the upper surface of the device during use and is substantially impermeable to the drug, and a release liner to protect the basal surface of the device prior to use. Optionally, a contact adhesive layer or a peripheral ring of contact adhesive may be provided on the basal surface of the device to enable adhesion of the device to the skin during drug delivery.

Novel drug reservoirs and transdermal systems are provided using these unique manufacturing methods.

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Brief Description of the Drawings

FIG. 1 illustrates in schematic form one embodiment of a solid matrix-type transdermal delivery system which may manufactured so as to contain a supersaturated drug reservoir as provided herein.

FIG. 2 illustrates in schematic form an alternative embodiment of a solid matrix-type transdermal delivery system which may be manufactured so as to contain a supersaturated drug reservoir as provided herein.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

By "transdermal" delivery, applicants intend to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream.

By a "supersaturated" drug reservoir, as used herein, is intended a reservoir containing an amount of drug molecularly dispersed therein at a concentration greater than the solubility of the drug in the reservoir material at room temperature. The term "molecularly dispersed" in this context is intended to mean that the drug is "dissolved" in the reservoir material as opposed to a solid phase present therein; typically, then, the molecular dispersion of drug in reservoir material provided using the present technique is a single phase of drug and reservoir material.

By an "effective" amount of a drug is meant a nontoxic but sufficient amount of the drug to provide the desired therapeutic or prophylactic effect. An "effective" amount of a permeation enhancer as used herein means an amount that will provide the desired increase in skin permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

By "predetermined area of skin" is intended a defined area of intact unbroken living skin or mucosal tissue. That area will usually be in the range of about 5 cm^2 to about 100 cm^2, more usually in the range of about 20 cm^2 to about 60 cm^2. However, it will be appreciated by those skilled in the art of transdermal drug delivery that the area of skin or mucosal tissue through which drug is administered may vary significantly, depending on patch configuration,

The reservoir components include a polymeric material, preferably comprised of a pressure-sensitive adhesive material, and a drug formulation. Additional components may be present as well, as will be explained below. A phase diagram of the selected polymeric material and drug formulation is constructed using conventional techniques, i.e., Differential Scanning Calorimetry (DSC) or hot stage polarized optical microscopy, and the depressed melting temperature of the polymer-drug composition is calculated therefrom. Basically, a series of samples with a range of drug concentrations is evaluated by measuring the depressed melting temperature for each sample. The depressed melting temperature is the temperature at which all of the drug is dissolved in the polymer phase; in essence, this is equivalent to determining solubility as a function of temperature.

The depressed melting temperature of any particular polymer-drug admixture is thus the temperature at which the drug is completely dissolved in the polymer phase, forming a single phase solution. If more than one polymeric material is used, the temperature is such that the drug forms a single phase solution with each of the polymeric materials.

An admixture of polymer and drug is then heated to a temperature just higher than the calculated depressed melting temperature, but not so high as to result in chemical alteration or degradation of any reservoir component. Generally, the temperature will be less than about 40°C greater than the depressed melting temperature, more typically less than about 10°C greater than the depressed melting temperature, and most typically less than about 5°C greater than the depressed melting temperature. Heating is continued until all of the drug is observed to dissolve in the selected polymeric material. As little as one or two minutes (or less)

typically less than about 10 wt.%, preferably less than about 5 wt.%, at the drug's melting temperature. This method will be particularly useful with silicone adhesives and polyisobutylenes. However, as above, each individual drug-polymer formulation will need to be evaluated independently to determine whether this method or the former method should be used.

Suitable polymeric materials for the drug reservoir are pressure-sensitive adhesives which are physically and chemically compatible with the drug to be administered, and the carriers and vehicles employed. Such adhesives include, for example, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether amide block polymers (e.g., PEBAX), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof. Presently preferred adhesive materials for use as reservoir layer are acrylates, silicones and polyisobutylenes. Also preferred are the reservoir materials described in commonly assigned U.S. Patent No. 5,252,334 to Chiang et al., i.e., combinations of acetate-acrylate copolymers (such as may be obtained under the trademarks GELVA® 737 and GELVA® 788 from Monsanto Chemical Co.) with a water soluble, water-absorptive polymer such as polyvinyl alcohol, gelatin, polyacrylic acid, sodium polyacrylate, methylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, gum acacia, gum tragacanth, carrageenan and gum guar, particularly polyvinylpyrrolidone. As explained above, however, when Method A is used, acrylic adhesives and polyurethanes are preferred materials for the reservoir; when Method B is used, as noted above, preferred adhesives are generally silicones and polyisobutylenes.

hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethisterone, norethynodrel, desogestrel, 3-keto desogestrel, gestadene and levonorgestrel; estrogens such as estradiol and its esters (e.g., estradiol benzoate, valerate, cyprionate, decanoate and acetate), ethynyl estradiol, estriol, estrone and mestranol; corticosteroids such as betamethasone, betamethasone acetate, cortisone, hydrocortisone, hydrocortisone acetate, corticosterone, fluocinolone acetonide, prednisolone, prednisone and triamcinolone; and androgens and anabolic agents such as aldosterone, androsterone, testosterone and methyl testosterone.

The drug formulation may include, in addition to drug, a solvent effective to facilitate dissolution of the drug. When Method A is used, it is preferred to use a solvent in which the drug have high solubility. The choice of solvent will thus depend on the drug, but, generally, ethyl acetate, toluene, and alcohols such as methanol, ethanol and isopropanol will be suitable. With Method B, the choice of solvent is somewhat less important; virtually any solvent can be used so long as it is relatively easy to remove and favors processability of the drug-polymer admixture. If a solvent is used, it is removed during or before heat treatment. The temperature at which the solvent is removed, and the time required for solvent removal will depend, clearly, on the volatility of the solvent used. Solvent removal may be effected in a single step, or a two-step process, in which different times and temperatures are involved in each step, may be used.

The drug formulation may also include standard carriers or vehicles useful for facilitating drug delivery, e.g., stabilizers, antioxidants, anti-irritants, crystallization inhibitors (such as

system which may be manufactured using the present technique is shown in FIG. 1. The composite, generally designated **10**, comprises a backing layer **11**, a reservoir layer **12** supersaturated with drug **12a**, and a release liner **13**. Such a structure is generally termed a "monolithic" transdermal system because the reservoir layer doubles as the adhesive which affixes the device to the skin.

The backing layer **11** functions as the primary structural element of the device and provides the device with much of its flexibility, drape and, preferably, occlusivity. The material used for the backing layer should be inert and incapable of absorbing drug, enhancer or other components of the pharmaceutical composition contained within the device. The backing is preferably made of one or more sheets or films of a flexible elastomeric material that serves as a protective covering to prevent loss of drug and/or vehicle via transmission through the upper surface of the device, and will preferably impart a degree of occlusivity to the device, such that the area of the skin covered on application becomes hydrated. The material used for the backing layer should permit the device to follow the contours of the skin and be worn comfortably on areas of skin such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the device disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. Examples of materials useful for the backing layer are polyesters, polyethylene, polypropylene, polyurethanes and polyether amides. The layer is preferably in the range of about 15 microns to about 250 microns in thickness, and may, if desired, be pigmented, metallized, or provided with a matte finish suitable for writing.

Any of the transdermal drug delivery devices manufactured using the present technique may also be provided with a release rate controlling membrane to assist in controlling the flux of drug and/or vehicle from the device. Such a membrane will be present in a drug delivery device beneath and typically immediately adjacent to the drug reservoir, and generally between the drug reservoir itself and an adhesive layer which affixes the device to the skin. Representative materials useful for forming rate-controlling membranes include polyolefins such as polyethylene and polypropylene, polyamides, polyesters, ethylene-ethacrylate copolymer, ethylene-vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene, polyacrylonitrile, ethylene-propylene copolymer, and the like. A particularly preferred material useful to form the rate controlling membrane is ethylene-vinyl acetate copolymer.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted

Skin permeation from vehicles: Modified Franz diffusion cells were used for evaluating the performance of vehicles for drug delivery. The receiver compartment was filled with 7.5 ml of pH 7 buffer. Two hundred μl of the selected vehicles saturated with drug were then placed into the donor compartment to initiate the skin flux experiments. The temperature of the diffusion cell contents was maintained at 32°C ± 1°C. At predetermined times, one ml of receiver content was withdrawn and replaced with fresh buffer. Samples were assays by HPLC.

Skin permeation from prototypes: Modified Franz cells were used for evaluating the prototype systems for drug delivery. The prototype systems were peeled off the polyester release liner and placed on top of the epidermis with the drug adhesive layer facing the stratum corneum. Gentle pressure was applied to insure full contact between the drug adhesive layer and the stratum corneum. The skin membrane with the prototype system was then mounted carefully between the donor and the receiver compartments. The receiver compartment was filled with pH 7 buffer and the temperature was maintained at 32°C ± 1°C throughout the experimental period. One ml of receiver content was withdrawn and replaced with fresh buffer. Samples were assayed by HPLC.

Flux determination: Skin flux ($\mu g/cm^2/hr$) was determined from the steady-state slope of the plot of the cumulative amount of drug permeated through the skin versus time. After steady state had been established, the linear portion of the plot was used to calculate the flux from the slope. Each formulation was run in triplicate, and the values reported represent the mean and standard deviation for three cells.

dissolved in adhesive as is evidenced by their transparent appearance. The 80 wt.% sample exhibited a melting temperature that is identical to that for the pure drug, within experimental error. A sample such as this is turbid after heating above the melting temperature, indicating a high concentration estradiol liquid phase has separated from the polymer phase.

Table 1. Melting Temperatures for Estradiol in DURO-TAK® 2287

Concentration of Estradiol (wt.%)	Melting Temperature (°C)
5	109
10	132
20	158
40	180
80	189
100	190

Example 2

Laminates with 5 wt.% estradiol in DURO-TAK® 87-2287 were prepared similar to the procedure in Example 1, coating onto the release side of 3-EST-A 242M film. Solvent was removed by drying in an oven at 70°C for one hour. The non-release side of a second piece of 3-EST-A 242M film was laminated to the adhesive to serve as a backing material. A portion of a 5 wt.% laminate was subjected to a heat treatment at 140°C ± 10°C for one hour. Note that this temperature is greater than the melting temperature for the 5 wt.% sample in Example 1 and is substantially less than the melting temperature of the pure drug.

Disks of the laminates were punched out with a die (3/8" for the heat-treated sample, 5/8" for the nonheat-treated samples). In addition, 5/8" disks of Silastic® membrane were also punched with a die. The release liner was removed from the sample and the

increase the amount of estradiol delivered across the Silastic® membrane by a factor of four.

Example 4

A sufficient amount of micronized estradiol hemihydrate was added to Silicone 4201 containing heptane in order to prepare a laminate with 20 wt.% estradiol in adhesive solids. The samples were mixed on a rotator overnight. The resultant mixture contained a dispersion of crystalline estradiol in wet adhesive. A laminate was drawn down on the release side of 1022 film with a knife at 15 mil wet. The solvent was removed by drying in an oven at 70°C for 1 hour. A portion of this laminate was heat treated in an oven at 185°C ± 10°C for 30 minutes and subsequently quenched to room temperature by removing it from the oven. Since the estradiol concentration in this sample is well above the solubility of the drug in Silicone 4201 at the drug melting temperature (0.8 wt.%, as determined by DSC), this sample was multi-phase following heat treatment. The heat-treated and nonheat-treated samples were run in the flux study described in Example 3. The results are displayed in FIG. 6, and reveal an order of magnitude increase in the amount of estradiol delivered across the Silastic® membrane.

Example 5

A sample of 20 wt.% estradiol in a PIB blend (see materials section, above, for further information) was prepared using a method identical to that described in Example 4, including the heat treatment of a portion of the sample. As in Example 4, the estradiol concentration in the sample was well above the solubility of the drug in PIB at the drug melting temperature (3 wt.%, determined by DSC). This sample was multi-phase following heat treatment.

Claims:

1. A method for preparing a supersaturated drug reservoir for incorporation into a transdermal drug delivery device, comprising: (a) admixing a polymeric material and a drug formulation compatible therewith to form a drug-polymer admixture; (b) evaluating the depressed melting temperature of the drug-polymer admixture; (c) heating the admixture prepared in step (a) to a predetermined temperature, effective to dissolve the drug in the polymeric material, wherein the predetermined temperature is above the depressed melting temperature calculated in step (b); and (d) cooling the heated admixture prepared in step (c) to form the drug reservoir,

wherein the relative quantities of drug and polymeric material are such that the drug reservoir contains on the order of 0.1 wt.% to 20 wt.% drug.

2. The method of claim 1, wherein the drug formulation contains a solvent effective to dissolve the drug.

3. The method of claim 2, further including, at some point prior to step (d): removing the solvent from the admixture.

4. The method of claim 3, wherein the polymeric material comprises a pharmaceutically acceptable pressure-sensitive adhesive.

5. The method of claim 1, wherein the drug is selected on the basis of its capability to phase separate into a low thermodynamic activity form.

6. The method of claim 5, wherein the low thermodynamic form is a crystalline structure.

phase comprising primarily polymeric material, and a second liquid phase comprising primarily drug formulation, wherein the predetermined temperature is such that it is higher than the actual melting temperature of the pure drug contained in the drug formulation; and (c) cooling the heated admixture prepared in step (b) to form the drug reservoir,

wherein the relative quantities of drug and polymeric material are such that the drug reservoir contains on the order of 0.1 wt.% to 20 wt.% drug.

11. A method for manufacturing a transdermal drug delivery device having a supersaturated drug reservoir, comprising: preparing a supersaturated drug reservoir in the form of a thin film having an area in the range of approximately 5 cm^2 to 100 cm^2, using the method of claim 1; laminating the thin film to a backing layer which defines the upper surface of the device and is substantially impermeable to the drug contained in the reservoir; and applying a layer of a pharmaceutically acceptable pressure-sensitive adhesive material to the thin film to serve as the basal surface of the device and the means for affixing the device to the skin during drug delivery.

12. A method for manufacturing a transdermal drug delivery device having a supersaturated drug reservoir, comprising: preparing a supersaturated drug reservoir in the form of a thin film having an area in the range of approximately 5 cm^2 to 100 cm^2, according to the method of claim 4; and laminating the thin film to a backing layer which defines the upper surface of the device and is substantially impermeable to the drug contained in the reservoir.

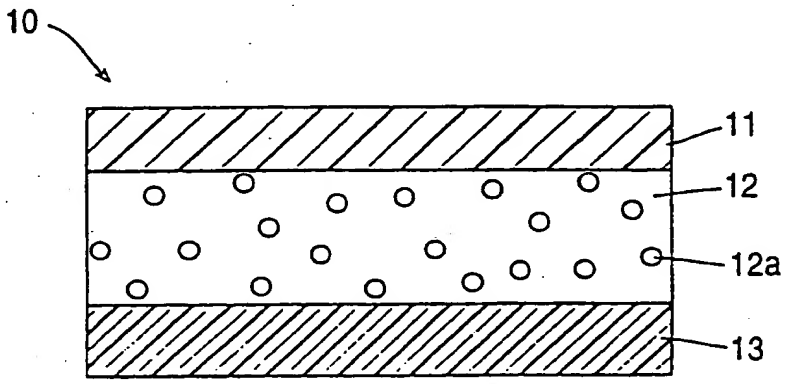

FIG. 1

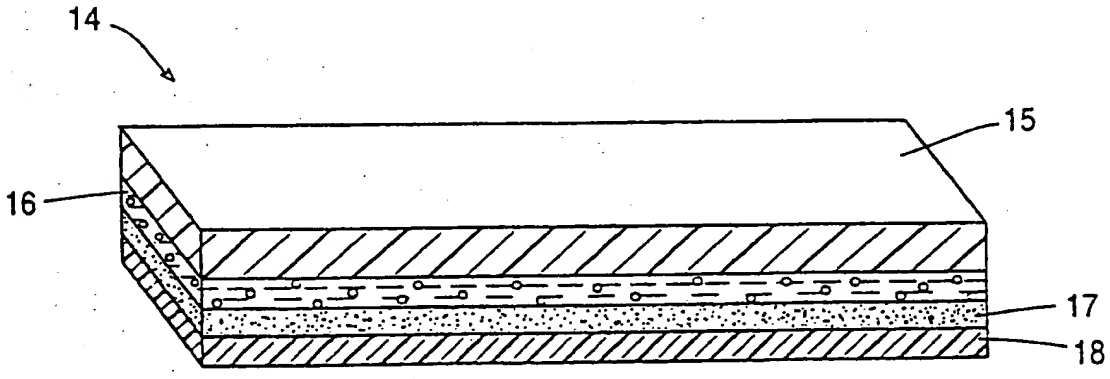

FIG. 2

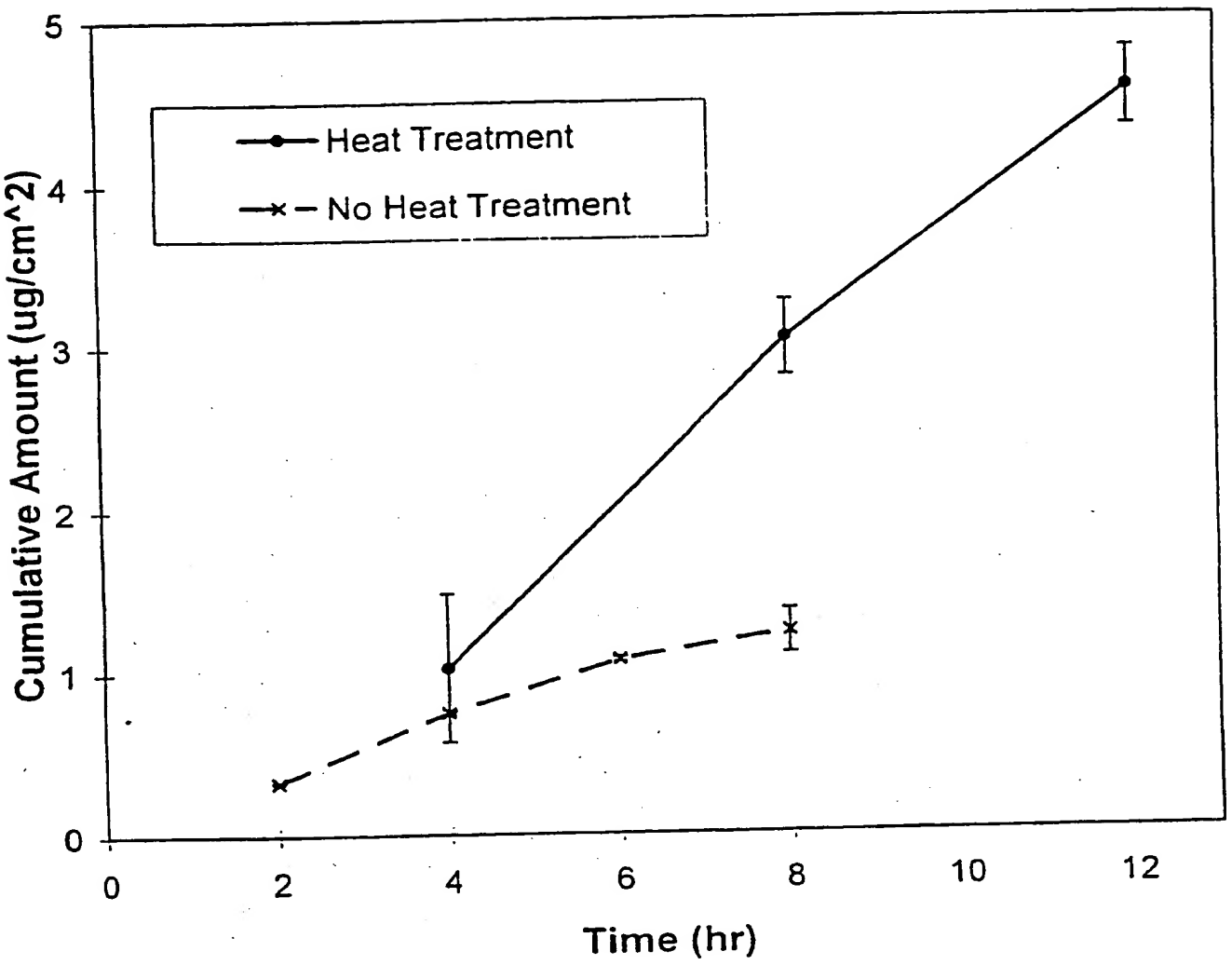
Heat Treatment
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FIG. 4

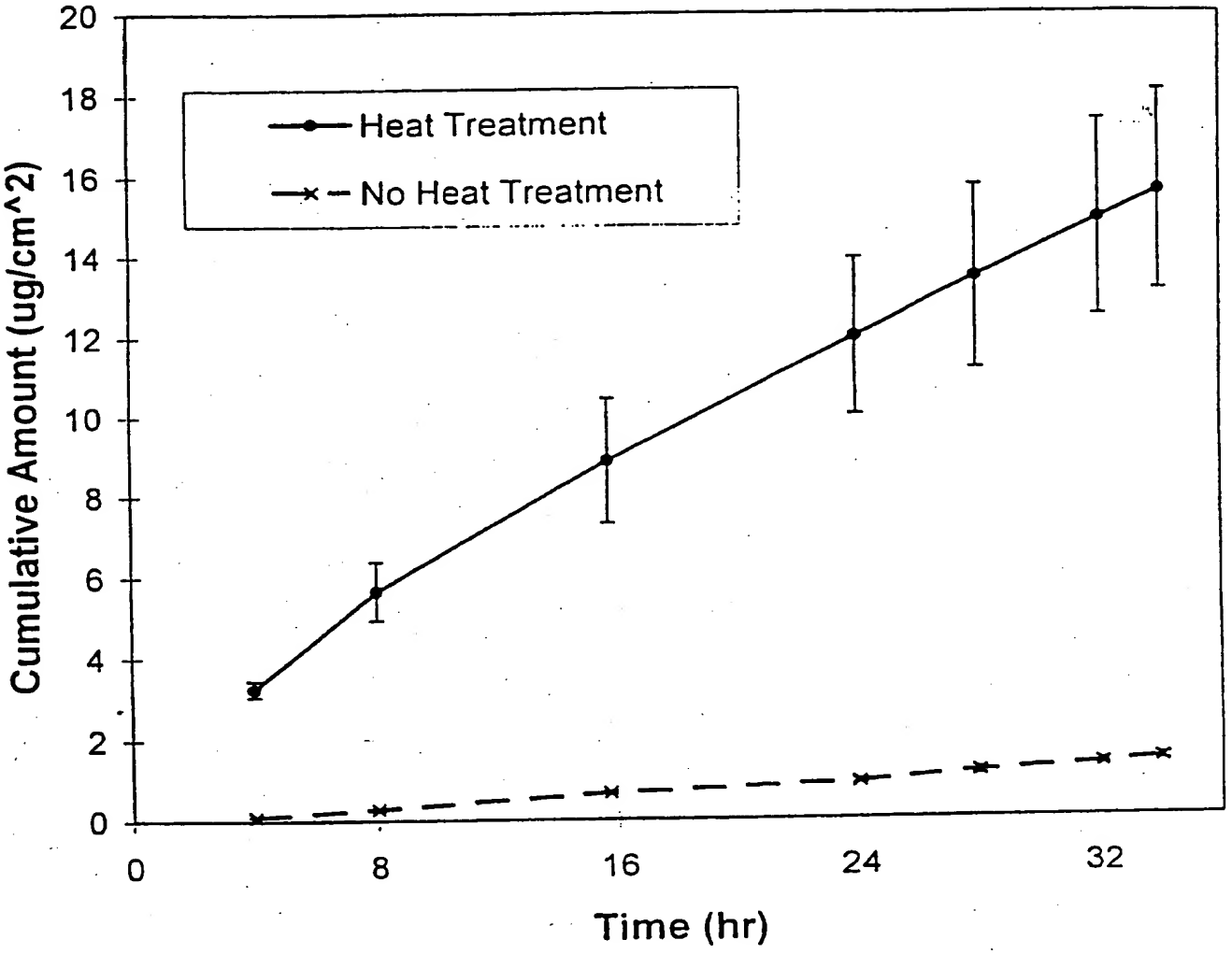
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FIG. 6

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/70

A3

(11) International Publication Number: WO 97/10812

(43) International Publication Date: 27 March 1997 (27.03.97)

(21) International Application Number: PCT/US96/14331

(22) International Filing Date: 6 September 1996 (06.09.96)

(30) Priority Data:

08/525,867	8 September 1995 (08.09.95)	US
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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 24 April 1997 (24.04.97)

(54) Title: SUPERSATURATED TRANSDERMAL DRUG DELIVERY SYSTEMS, AND METHODS FOR MANUFACTURING THE SAME

(57) Abstract

Methods are provided for manufacturing transdermal drug delivery systems containing supersaturated drug reservoirs, such that higher drug fluxes are obtained. The methods involve heating the drug reservoir components to a predetermined temperature. Generally, this temperature is higher than the depressed melting temperature of the polymer-drug admixture which will serve as the drug reservoir. In an alternative embodiment, wherein heat treatment of the reservoir components results in a system having two liquid phases, the predetermined temperature is calculated so as to be higher than the melting temperature of the pure drug. Drug reservoirs and novel transdermal delivery systems prepared using the disclosed techniques are provided as well.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 96/14331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 144 486 A (LOHMANN GMBH & CO KG ;SANOL ARZNEI SCHWARZ GMBH (DE)) 19 June 1985 see the whole document ---	1-9, 11-15
X	WO 92 05811 A (ETHICAL PHARMA LTD) 16 April 1992 see the whole document ---	1-15
X	JOURNAL OF CONTROLLED RELEASE, vol. 17, no. 3, 1991, A61K9/70B, pages 225-234, XP000236563 AKTHAR ET AL.: "The influence of crystalline morphology and copolymer composition on drug release from solution cast and melt-processed P(HB-HV) copolymer matrices." see the whole document ---	1-6,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 March 1997	21. 03. 97

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national Application No
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